Clinical trial diversity policy drivers

FDA diversity policy: past, present, and future

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Diversity in clinical development

Studies have suggested that people included in pivotal studies for drug approval do not reflect the diversity of the US population

Over a decade of initiatives by the FDA, the NIH, and other private and public institutions and legislation

Obstacles – recruiting patients, participation criteria, trial design, and expected efficacy

What else is necessary: policy change, regulation, private investment, incentives community action?

FDA initiatives to achieve more accurate representation in clinical studies

Over a decade of activity and goal setting to achieve greater diversity

2011

- Dialog, hosted by Society for Women's Health Research and the FDA, proposes:
  - Increasing the number of women and minority investigators
  - Community engagement, education
  - Communication

2012

- Food and Drug Safety Innovation Act (FDASIA) – Section 907:
  - Required the FDA to produce a report regarding "inclusion of demographic subgroups in clinical trials and data analysis in applications for drugs, biologics, and devices"

2013–2014

- Report released finding:
  - Whites overrepresented and minorities underrepresented in trials relative to US population
- Action plan set forth priorities focused on data collection and overcoming barriers

2017–2018

- Food and Drug Administration Reauthorization Act (FDARA) – Section 610:
  - Required the FDA to convene a public workshop on clinical trial eligibility criteria
- Workshop held and proposed reforms to communication, trial design, expanded access programs

2020

- Final guidance:
  - Recommendations on how clinical trial sponsors can approach enrollment of underrepresented patient populations

2022

- Draft guidance
  - Establishing diversity plans to improve enrollment of participants from underrepresented racial and ethnic populations in clinical trials

2023

- Guidance is no longer draft
  - The FDA will be required to finalize guidance in 2023
  - Biopharma companies will need to submit a "diversity plan" in pivotal studies

Pivotal clinical trials do not reflect US population diversity today: Progress check

Progress check (comparing pivotal trial enrollment to US census in 2019)

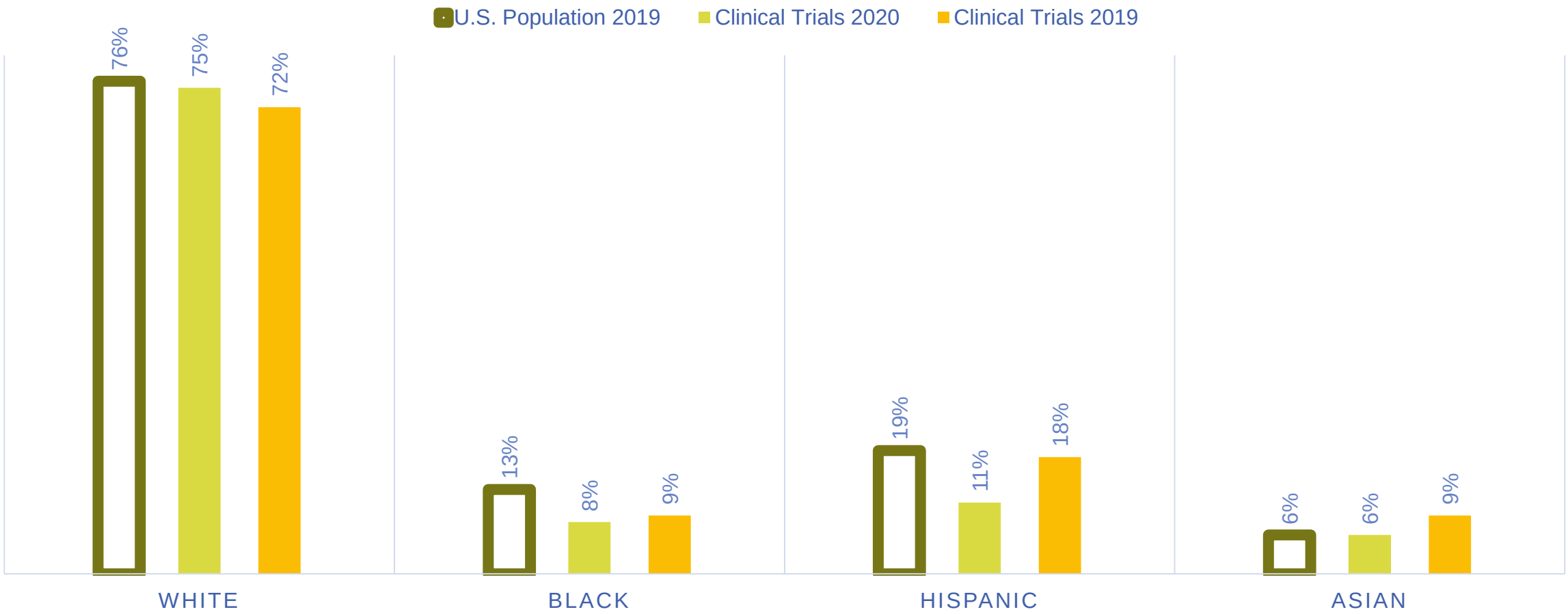
FDA Drug Trials Snapshot reports

- 48 new drugs approved
  - 2 enrolled Blacks and Latinos at population benchmark
- 53 new drugs approved
  - 6 enrolled Blacks and Latinos at population benchmark
- 50 new drugs approved
  - 5 enrolled Blacks and Latinos at population benchmark
- 37 new drugs approved
  - 2 enrolled Blacks and Latinos at population benchmark

Pivotal clinical trials do not reflect US population diversity today

FDA Drug Trials Snapshot (considering trials with 50 percent or more of the population from the US)

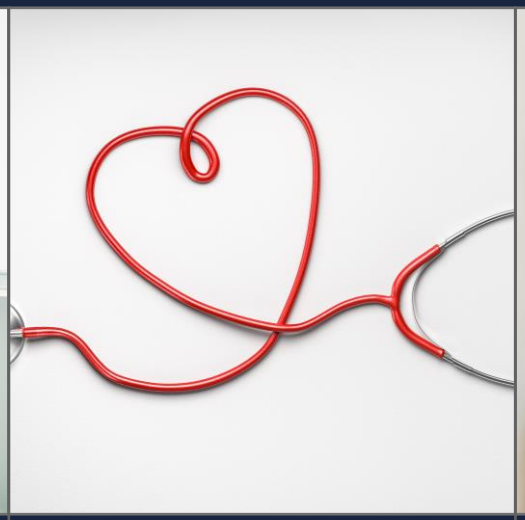
US Census compared to FDA Drug Trials Snapshot



Obstacles to accurate representation in trials

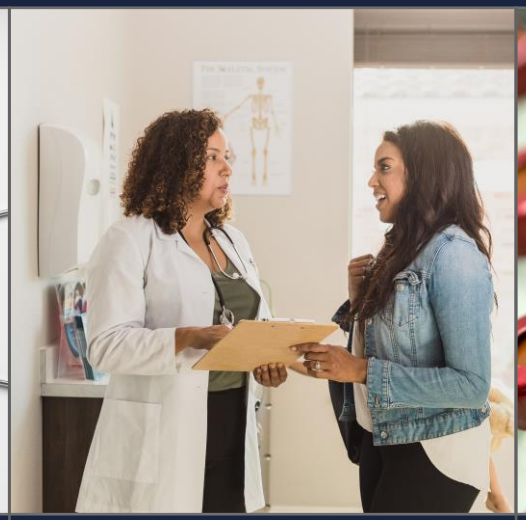
Recruiting patients

- Communication
- Incentives and renumeration
- Travel to sites
- Retention
- Insurance coverage



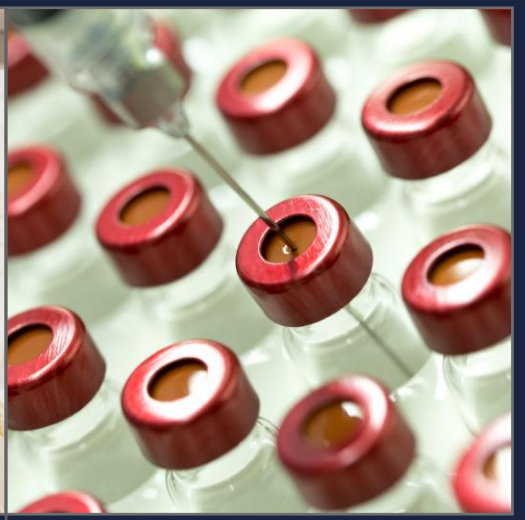
Inclusion/exclusion criteria

- Hypertension, CV risk
- Mental health
- Multiple comorbidities
- Perceptions of ability to complete



Trial design

- Remote enabled
- Location
- Patient input
- Endpoints

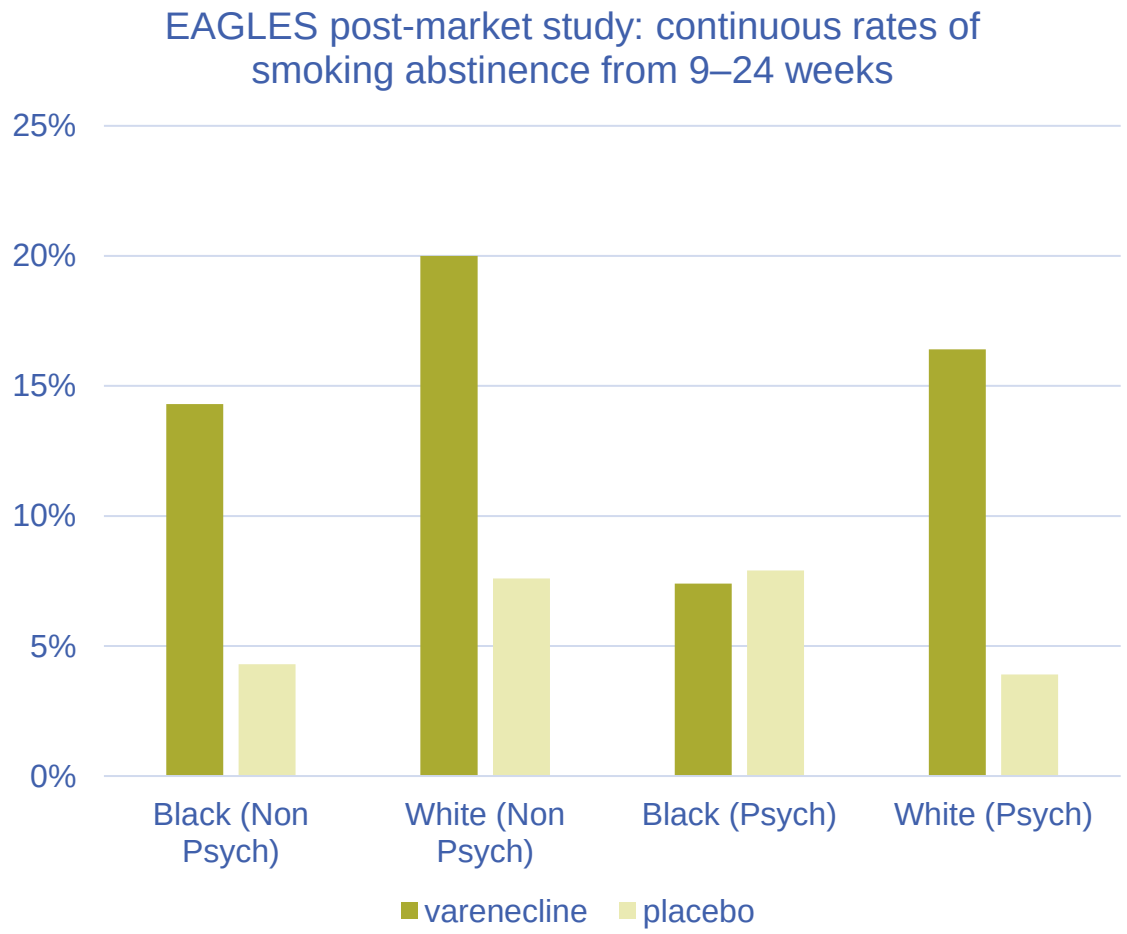


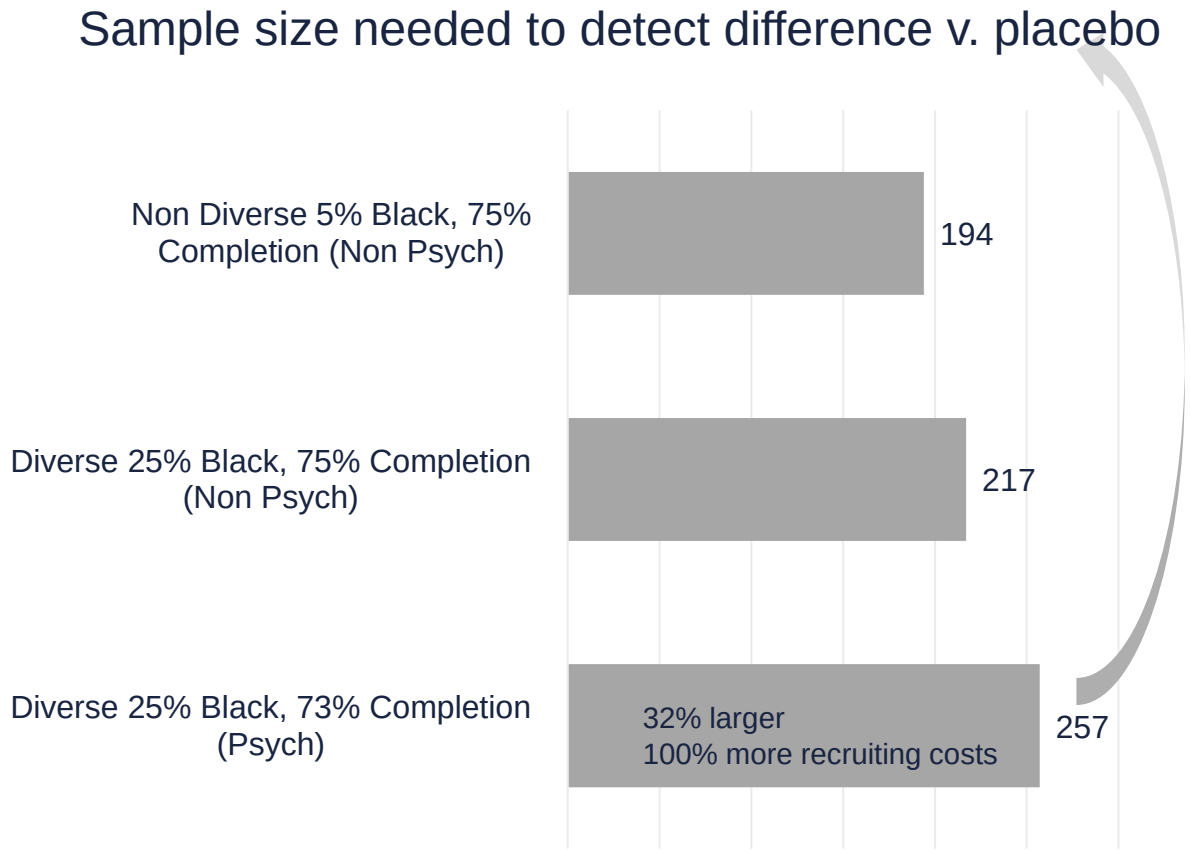
Expected efficacy

- Severity of underlying condition
- Response to treatment
- Adaptive trial designs

Case study: expected efficacy and retention impact on size and cost of trials

Example from smoking cessation treatment





5% significance, 80% power hypothetical, size for one group (will need 2x that number to include placebo and active)

Guidance encourages sponsors to integrate diversity

Draft guidance issued to industry clinical trial sponsors encourages a plan to enroll a representative population and analyze data for specific groups

Broad range of focus

- Encourages development of a diversity plan for a broad range of medicines and devices

As early as is feasible

- Recommends submitting no later than when the sponsor is seeking input on the pivotal trial design
- Emphasizes strategies to enroll a representative population and potential challenges
- If a diversity plan does not work, the sponsor should engage with the FDA to plan for post-market data collection

Content of submission

- Overview of the disease and specific impact on certain populations
- Enrollment goals for the study population by race and ethnicity considering epidemiology
- Data on differential efficacy in certain populations
- Information about differences in data collection approaches based on race (*eg*, pulse oximeter readings and skin pigmentation)
- Plan to assess data collected by race and ethnicity

FDA: Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials, April 2022, FDA-2021-D-0789

Shift from guidance to a requirement for a "diversity plan" in pivotal clinical studies

Consolidated Appropriations Act 2023: Summary of legislative text

Requires drug trial sponsors to submit a diversity action plan with protocol for a phase-3 study

- Enrollment targets, plan to achieve, and reporting
- Exception for diseases where it is not feasible (*eg*, rare diseases)
- No enforcement mechanism

Requires the FDA to finalize currently draft clinical trial diversity guidance…

…and issue 3 new guidance on clinical trial modernization: decentralized trials, electronically enabled trials, and innovative designs

Requires the HHS to hold a public workshop to seek input on increasing enrollment of underrepresented groups…

…in partnership with industry, academia, and advocates

Requires the HHS to report on efforts and outcomes of diversity action plans

NIH Clinical Trial Diversity Act 2022

Under consideration by Congress (House and Senate, bipartisan)

Summarized from S. 5268 and H.R.7845

Standards for government-funded research

- Requires researchers with NIH funding to:
  - Have a defined plan to achieve accurate representation
    - Race, ethnicity, sex, age
  - Describe how they will analyze distinct population groups
  - Implement the least burdensome patient protocol
    - Or explain if not feasible
  - Provide metrics on enrollment by population group

Eliminate cost barriers

- Requires the HHS to produce a study evaluating need to update regulations including:
  - Reimbursement for participation expenses
  - Compensation for human subjects

Education campaign

- Requires the HHS to carry out a national awareness campaign about clinical trial participation and the need for participation by diverse communities
- Provides grants to nonprofits to test outreach strategies

Post-marketing approaches to obtain data

August 2023 FDA draft guidance

Populations underrepresented in clinical trials for drugs and biological products

According to the FDA, pre-market clinical trials should represent all relevant ages, genders, and racial and ethnic groups	Draft guidance encourages early engagement with agency in pre-market study design
When populations in a pre-approval clinical study are not representative, the FDA may request or require post-market data collection	**Post-marketing requirements (PMR):** Regulations that require an applicant to conduct a post-market study assessing the rate of adverse events in particular races or ethnic minorities if there is evidence to suggest the risk is higher for those populations **Post market commitment (PMC):** Where there may be a risk or differential efficacy for a certain racial or ethnic subgroup, the FDA may enter into an agreement with the applicant to collect additional evidence after the drug is approved Approaches include single-arm trials, randomized controlled trials with stratification, real-world evidence including registries, or meta-analyses where data is pooled across trials
The FDA may approve drugs based on an entirely extraterritorial clinical development program and population	The FDA may ask for additional evidence in a US study

Data for approved drugs does not reflect the racial and ethnic distribution of the US population; consider incentives

Over a decade of initiatives by the FDA, the NIH, and other private and public institutions

Obstacles – recruiting patients, participation criteria, trial design, expected efficacy

Guidance or plans may not be enough

Proposed incentives to stimulate focus

- Priority review/vouchers
- Fast-track designation
- Extended data exclusivity

Consider existing incentives for priority populations

Could they be used to support trial diversity?

	Current uses	Potential to encourage diversity
Fast-track	For drugs in development that are likely to address a significant unmet need in a serious condition. Allows for early and more frequent communication with the FDA. Sponsor applies with the IND, or requests to test the drug in humans for a clinical study, the sponsor finds doesn't know it will be granted	Extra and early meetings may help address concerns about effect size, innovative trial designs, or inclusion and exclusion criteria Meetings and communication may not be a large enough incentive, particularly if the trial outcome is uncertain Fast-track status is not known at time of trial design
Priority review (voucher)	For potential drugs that are aimed at treating serious conditions, and that are considered improvements when compared to existing therapies. Priority review reduces drug review time by six months (or a voucher can be sold). The FDA decides whether there will be priority review at the time of the new drug application (the BLA, NDA) which occurs after the pivotal clinical studies are complete for an investigational new drug (the IND). The sponsor may request priority review	Faster review has a direct financial benefit that could stimulate investment in diversity in the study Issuing more priority review vouchers may decrease their value Uncertain when trials are being conducted if granted
Extended data exclusivity	Currently used for pediatric studies and applies to a broad range of new drugs. The FDA can ask for extended data exclusivity, or sponsor can ask for a trial in a certain population – they are not forced. The trial does not need to show efficacy or superiority. If the sponsor conducts the studies agreed to with the FDA, they are granted an additional six months of protection of their clinical data – essentially without generic competition at the end of market exclusivity	Provides significant financial incentive to invest in clinical evidence Certainty if granted; investment occurs after designation Increases post-market data collection, but not pre-market

Discussion topics

How are companies preparing for diversity plans?

What policy would enable success?

What is the role of technology and new approaches in conducting trials?

How should real-world evidence or post-market studies be used to demonstrate safety and efficacy on typically underrepresented populations?

Should incentives be considered?

Collaboration v. individual efforts to recruit and retain

Panel discussion

Accurate representation in clinical study: why it matters, why it is hard, and what types of policy change would make it more achievable?

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